



Should formula for infants provide arachidonic acid along with DHA? A position paper of the European Academy of Paediatrics and the Child Health Foundation

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1 **Choices for adding long-chain polyunsaturated fatty acids to infant formula.**

2 **A position paper of the European Academy of Pediatrics and the Child Health Foundation**

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66

67

68 **Abstract** (244 words)

69 Recently adopted regulatory standards on infant and follow-on formula for the European Union stipulate
70 that from 2021 onwards, all such products marketed in the European Union must contain 20-50 mg/100 kcal
71 of omega-3 docosahexaenoic acid (DHA), which is equivalent to about 0.5-1 % of fatty acids and thus higher
72 than typically found in human milk and current infant formula products, without the need to also include
73 omega-6 arachidonic acid (ARA). This novel concept of infant formula composition has given rise to concern
74 and controversy since there is no accountable evidence on the suitability and safety in healthy infants.
75 Therefore, international experts in the field of infant nutrition were invited to review the state of scientific
76 research on DHA and ARA, and to discuss the questions arising from the new European regulatory
77 standards. Based on the available information, we recommend that infant and follow-on formula should
78 provide both DHA and ARA. The DHA should equal at least the mean content in human milk globally (0.3 % of
79 fatty acids) but preferably reach a level of 0.5 % of fatty acids. While optimal ARA intake levels remain to be
80 defined, we strongly recommend that ARA should be provided along with DHA. At current formulas DHA
81 levels and up to about 0.64%, ARA contents in formulae for infants should at least equal the DHA contents.
82 Further well-designed clinical studies should evaluate the optimal intakes of DHA and ARA in infants at
83 different ages based on relevant clinical outcomes.

84 .

85 **Key Words:** infant nutrition, breast milk substitutes, long-chain polyunsaturated fatty acids (LC-PUFA),
86 European Commission Formula Delegated Act 2016/127, food safety

87

88

89 Introduction

90 Breastfeeding, which is universally recommended as the optimal choice of infant feeding, always supplies
91 both the long-chain polyunsaturated fatty acids (LC-PUFA) docosahexaenoic acid (omega-3 [n-3] DHA, 22:6n-
92 3) and arachidonic acid (omega-6 [n-6] ARA, 20:4n-6) (1-3). Many studies have evaluated outcomes in infants
93 fed infant and follow-on formula containing the n-3 fatty acid DHA at levels from 0.1 to 0.5 % of total fatty
94 acids together with the n-6 fatty acid ARA, usually with higher ARA levels than those of DHA. Many infant
95 and follow-on formulas include DHA and ARA close to median worldwide levels of these fatty acids in human
96 milk (~0.3 and 0.5% of total fatty acids, respectively) (1). Infant formulas with both DHA and ARA have been
97 widely used worldwide for nearly 20 years without any serious concern for their safety, and benefits have
98 been reported in some but not in all studies (4-6). In 2016 the European Commission adopted legislation on
99 Infant and Follow-on Formula in the form of a Delegated Act, which stipulated that by February 2021 all
100 infant and follow-on formula marketed in the European Union must contain DHA at higher levels than in
101 currently marketed infant formulas (20-50 mg/100 kcal, approximately 0.5-1% of total fatty acids) without
102 any requirement for also providing ARA (7). The European legislation also stipulates that the content of the
103 omega-3 fatty acid eicosapentaenoic acid (EPA, 20:5 n-3) shall not exceed that of DHA, based on the advice
104 of a preceding opinion paper of the European Food Safety Authority (EFSA) which emphasized that EPA
105 contents in human milk are low and do not exceed those of DHA (8). The European legislation also rules that
106 the content of ARA shall not exceed 1% of the total fat content, and the content of all n-6 long-chain
107 polyunsaturated fatty acids together shall not exceed 2 % of total fat, which is not based on a
108 recommendation of EFSA (9) but on the previous European Directive on infant and follow-on formula
109 adopted in 2006 (10). Following the new regulation, the first commercial formula products with high
110 contents of DHA and without ARA have been recently introduced in Europe.

111 This novel concept of infant formula composition proposed by the recent European legislation, with
112 relatively high mandatory contents of DHA but no need to provide ARA, has raised considerable concern and
113 controversy because there is no accountable documentation of the suitability and safety of this new
114 approach (11-14).

115 Therefore, the charitable Child Health Foundation (Stiftung Kindergesundheit, www.kindergesundheit.de), in
116 collaboration with the European Academy of Paediatrics (www.eapaediatrics.eu), invited experts in this area,
117 including previous members of the NDA panel of EFSA and of the EFSA Working Group on Dietetic Products
118 involved in the scientific report (9) on which the recent legislation has been based (7), along with
119 representatives of an international organisation of parents, to review these questions at a workshop held on
120 24 to 25 May, 2019 at Berg near Munich, Germany. Here we report our key considerations and conclusions.

121

122 **Previous guidance on DHA and ARA supply in infancy**

123 Several bodies have provided recommendations on the desirable intakes of DHA and ARA in infancy and
124 early childhood, based on reviews of the existing evidence. Consistent across these bodies was consensus in
125 recommending the provision of both DHA and ARA, and for the content of DHA not to exceed the content of
126 ARA. For example, a joint report of the Food and Agriculture Organisation of the United Nations and the
127 World Health Organisation concluded there is convincing evidence to define adequate intakes for ARA of 0.2-
128 0.3 % of energy intake (E%, about 11-33 mg ARA/100 kcal), and for DHA of 0.10-0.18 E% (about 11-20 mg
129 DHA/100 kcal) (15). The Health Council of the Netherlands set an adequate daily intake for ARA of 40 mg/kg
130 bodyweight (bw) and for DHA of 20 mg/kg bw for infants aged 0 to 5 months (16). The French Food Safety
131 Agency set an adequate intake for ARA of 0.5 % of total fatty acids (about 24 mg ARA/100 kcal), and of DHA
132 of 0.32 of total fatty acids (about 16 mg DHA/100 kcal) for infants aged 0 to 6 months (17). In 2013, EFSA
133 defined adequate daily intakes for infants aged 0-6 months as 100 mg DHA and 140 mg ARA, while 100 mg
134 DHA was recommended for the age range of 6-24 months and 250 mg DHA + EPA at the age range of 24-36
135 months (8).

136 In 2009 EFSA concluded that a cause and effect relationship has been established between the intake of
137 infant and follow-on formula supplemented with DHA at levels around 0.3% of total fatty acids and
138 visual function at 12 months in in term infants fed formula up to 12 months, including breastfed infants

139 fed formula after weaning up to 12 months, and it recommended that a health claim should be adopted with
140 the wording “DHA contributes to the visual development of infants” (18).

141 With respect to the composition of infant formula, the previous European legislation on infant and follow-on
142 formula stipulated the optional inclusion of DHA and ARA provided that the content of DHA does not exceed
143 that of ARA (10). A further requirement was that EPA content does not exceed DHA content, and total n-3
144 and n-6 LC-PUFA contents do not exceed 1% and 2% of total fat content, respectively (10). Similarly, the
145 global Standard of the Codex Alimentarius Commission of the Food and Agriculture Organisation of the
146 United Nations and the World Health Organisation on infant formula and formulas for special medical
147 purposes intended for infants stipulates the optional inclusion of DHA in infant formula, provided that ARA
148 reaches at least the same concentration as DHA, while EPA should not exceed the DHA content (19).

149 Similar conclusions were drawn by international expert groups who advised that infant formula for infants
150 born at term should provide 0.2-0.5 % of fatty acids as DHA along with at least the same contents of ARA
151 (20), or at least 0.3 % of fatty acids as DHA along with ARA (21). An expert group advising the Codex
152 Alimentarius Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU) concluded that optional
153 addition of DHA should not exceed levels of 0.5% of total fat intake which has not been documented to be
154 safe in clinical trials in healthy infants, and ARA contents should reach at least the DHA contents, whereas
155 the EPA in infant formula should not exceed the DHA content (22). It also emphasized that there is no
156 sufficient documentation of the benefits and safety of the addition of DHA to infant formula at levels above
157 0.5% of total fat content, or of DHA without concomitant addition of ARA; such formula composition was
158 therefore expressively discouraged (22).

159 In conclusion, these previous guidance documents support the provision of both DHA and ARA to infants,
160 with intakes of ARA reaching at least those of DHA. Some of these reports also emphasized that metabolism
161 and fatty acid needs during infant development are uniquely different from adult principles, and that
162 knowledge of the metabolism and roles of these fatty acids in adults should not be directly extrapolated to
163 infants.

164 In contrast to these reports, an EFSA scientific opinion published in 2014 (9) concluded that DHA should be
165 added to infant and follow-on formulae in amounts similar to those provided to breast fed infants and
166 meeting the adequate intake of 100 mg/day previously established by EFSA, but it considered the provision
167 of ARA unnecessary even in the presence of DHA, even though only one year before EFSA had set the
168 adequate daily ARA intake for infants in the first half year of life as 140 mg (8).

169

170 **ARA supply during development**

171 We reviewed the sources of ARA available to the developing fetus and infant from placental uptake and
172 transfer from the mother, and from postnatal consumption of human milk. DHA and ARA are preferentially
173 supplied to the fetus compared to other fatty acids in the maternal circulation; however, ARA transfer, unlike
174 DHA, apparently is not related to maternal ARA status and intake (23, 24). Similarly, human milk always
175 supplies both ARA and DHA; in contrast to DHA, the content of ARA in human milk is much less variable and
176 always near 0.5 % of milk fatty acids, and typically higher than DHA (1-3, 25). We can only speculate about
177 the physiological relevance of this rather stable ARA provision to the fetus and infant, along with a more
178 variable DHA supply. It is noteworthy that significant amounts of ARA, along with some other n-6 LC-PUFA,
179 accumulate in the membranes of organs and tissues. Adrenic acid (ADA, 22:4n-6), an elongation product of
180 ARA, is a significant component in all membranes studied to date. For example, in brain both n-3 and n-6 LC-
181 PUFA (to an even greater extent) accumulate rapidly in the last intrauterine trimester and exponentially
182 during the first two years of postnatal life (26, 27). During this period of rapid early development, the ratio of
183 ADA to ARA in brain continues to increase such that by two years of age, ADA constitutes nearly half of the
184 n-6 LC-PUFA in brain, and n-6 LC-PUFA exceed n-3 LC-PUFA content by far (14).

185

186 **Possible importance of ARA supply with infant formulas**

187 Several studies have evaluated n-6 LC-PUFA status in infants fed formulas with and without DHA and ARA,
188 comparing results with those of infants fed human milk. These data demonstrate that both term and

189 preterm infants fed formula without ARA have declining ARA status, compared to human milk fed infants.
190 First reported in 1982, term infant formulas without LC-PUFA resulted in approximately half the amount of
191 ARA in infant red blood cell (RBC) phosphatidylcholine (PC) (28). Surprisingly, a 3-fold increase in linoleic acid
192 (18:2n-6) in one of the two infant formulas resulted in the lowest ARA percentage in RBC PC (28). A recent
193 study in term infants compared formulas without and with ARA (0 or 34 mg/100 kcal) and DHA (17 mg/100
194 kcal) and found less than half the amount of ARA (weight%) in plasma of infants fed the formula without
195 ARA, compared to the formula with ARA (29). Lymphocyte ARA was also affected, and the authors proposed
196 that ARA supply may have an immunoregulatory role on B-cell activation. The role of ARA in immune
197 ontogeny is supported by the finding that for every one mol% decline in whole blood ARA in the postnatal
198 period of preterm infants, there is a 40% increase in the risk of nosocomial sepsis (30). Furthermore, preterm
199 infants diagnosed with retinopathy of prematurity, a disease characterized by dysregulated immune and
200 inflammatory responses, demonstrated lower serum ARA levels compared to infants without this diagnosis
201 (31).

202 Human milk fed term infants have approximately 75 mg ARA/L in plasma PC shortly after birth, an amount
203 that is similar in infants born preterm. In preterm infants fed formulas without ARA, the concentration in
204 plasma PC declines to approximately 40 mg/L and remains low from term corrected age until approximately
205 6 months later, before gradually increasing over the next 6 months (32). If the formula provides n-3 LCPUFA
206 (0.2% DHA, 0.3% EPA) without ARA, the plasma PC ARA concentration declines further to approximately 30
207 mg/L (32). In contrast, preterm infants fed formulas with 0.43% ARA and 0.1% DHA from soon after birth
208 until 12 months corrected age (CA) have a plasma PC ARA concentration like infants fed human milk during
209 the same months. These data indicate that the the addition of both LC-PUFAs to infants formulas is
210 necessary to match circulating levels of DHA and ARA of breastfed infants (13).

211 ARA availability has been associated with growth of cells *in vitro* and of human infants *in vivo* (33, 34). Birth
212 weight of preterm infants was significantly correlated with plasma ARA contents (34). In preterm infants,
213 ARA concentration in plasma PC was a significant predictor of normalized weight and length achievement
214 during the first year of life at all five ages assessed (2, 4, 6.5, 9 and 12 months CA); and higher PC ARA

215 predicted larger head circumference at 2 and 4 months CA (35). The two highest quartiles of plasma PC ARA
216 were associated with infant weight and length achievement near the 50th percentile for term infants,
217 whereas infants in the two lower quartiles achieved mean weight and length gains that were one standard
218 deviation lower (35). In another randomized controlled trial (RCT) in 194 premature infants given preterm
219 formula with no DHA or ARA, with 0.15% energy DHA, or with 0.14% DHA + 0.27% ARA, infants fed DHA+ARA
220 formula gained weight significantly faster than control infants (34.7 vs. 30.7 g/day) (36). The review of
221 review of 32 randomized studies, 13 in preterm infants and 19 in term infants, indicate that the supply of n-
222 3 LC-PUFA without n-6 LC-PUFA can reduce growth achievement in preterm and term infants, although the
223 reported effect sizes are often modest (37).

224 While there is no conclusive evidence from RCTs in infants born in term comparing effects of formula feeding
225 without and with ARA on infant growth, the available data suggest that dietary ARA supply may be a relevant
226 modulator of physiological growth in infancy.

227

228 **Impact of genetic variability**

229 Common variants in the fatty acid desaturase (*FADS*) gene cluster modify the activity of polyunsaturated
230 fatty acid (PUFA) desaturation and the composition of human blood and tissues lipids (38). *FADS*
231 polymorphisms show large effect sizes on plasma and tissue levels of ARA and other n-6 PUFA, whereas
232 there are only small and in most studies non-significant effects on DHA and other n-3 PUFA (39). Infants with
233 genetic *FADS* variants predicting a low activity of the delta-5 and delta-6 desaturating enzymes comprise
234 about one quarter of the infant population in Europe, but about two thirds to three quarters of infants in
235 Asia and Latin America (40). In these infants with genetically determined low desaturase activity, ARA
236 synthesis is ineffectice, therefore they develop particularly low plasma ARA levels without a dietary supply of
237 preformed ARA (41). Genetic *FADS* variants are also associated with important health related outcomes such
238 as plasma lipid concentrations, eczema, and cognitive function (39). Studies on variations in the *FADS* gene
239 cluster provide impressive indications for marked gene-diet interactions in the modulation of complex

phenotypes such as eczema, asthma and cognition, with some studies indicating that breastfeeding providing both preformed ARA and DHA reduced asthma risk and improved cognitive outcomes in those infants with a genetically determined low formation of LC-PUFA (39). Given that genetic *FADS* variants influence primarily the formation of ARA and other n-6 LC-PUFA and have only little effect on DHA and other n-3 LC-PUFA, it appears likely that the provision of preformed ARA with breastfeeding is important for asthma risk reduction and improved cognitive development at least in infants with genetically low ARA synthesis. Due to the major differences in genotype distribution and PUFA metabolism, it seems inappropriate to extrapolate PUFA effects observed in infant populations with predominantly European or African genotypes to populations with genetically more frequent low desaturase activities, such as in Asian and Latin American populations.

250

251 **How much ARA do infants and young children receive from food?**

A review of the worldwide dietary supply of DHA and ARA shows wide variability of intakes, with particularly low dietary DHA and ARA intakes found in some studies in lower income countries (42, 43). The estimated daily dietary intake of ARA from food in infants older than 6 months and in young children evaluated in 76 countries of the developing world was 65 mg/day, with the major part provided by human milk. In this study, the lowest tertile for ARA intake has a higher prevalence of childhood stunting and higher infant mortality (43). Infants in the US KUDOS cohort had median ARA intakes from food of only 4 and 20 mg/day, respectively, at 9 (n=190) and 12 (n=201) months of age (S. Carlson, personal communication, 2019). Belgian preschool children had a mean ARA intake of only 17 mg/day (44). It is evident that infants will not achieve the adequate dietary intake of 140 mg/day as set by EFSA (8) unless they are fed human milk or an infant formula providing ARA.

262

263 **Ratio of DHA to ARA in formula influences n-6 LC-PUFA in brain and appears to have functional** 264 **consequences**

265 Effects of adding DHA and ARA to infant formula on neurodevelopmental outcomes have been described in
266 some but not in other studies (4). Infant formulas with different amounts of DHA and ARA were evaluated in
267 both baboons and human infants, including formulas without LC-PUFA, or with both ARA (~0.7% of total
268 fatty acids or ~34 mg/100 kcal) and different DHA levels, providing DHA to ARA ratios of 0.5:1 and 1.5:1 (45,
269 46). Human infants also received a fourth formula with a DHA to ARA ratio of 1:1 (46). Brain n-3 and n-6
270 LCPUFA were measured in various organs and brain regions in baboon infants (45). In baboons, plasma and
271 RBC ARA increased in both the LCPUFA-containing formulas; however, the increase was smaller at a DHA to
272 ARA ratio of 1.5:1. The highest ratio of DHA to ARA (1.5:1) induced a decrease in brain contents of ARA as
273 well as in n-6 ADA and n-6 docosapentaenoic acid (DPA, 22:5n-6), with DPAn-6 showing the greatest
274 decrease.

275 Human infants fed the formula with a DHA to ARA ratio of 1.5:1, like baboon infants, also showed a decrease
276 in red blood cell ARA, with levels more similar to the group fed formula with no LC-PUFA (47). Cognitive tests
277 of these four groups of infants up to 9 years of age showed a similar pattern, with less favourable outcomes
278 in infants randomized to a formula with a high DHA to ARA ratio: the group fed the 1.5:1 ratio of DHA to ARA
279 generally performed less well than the other two supplemented groups (46). On sustained attention in the
280 first year of life, a test of rule learning requiring inhibition between 3 and 5 years, and on verbal IQ at 5 and 6
281 years of age, the children fed formulas with a DHA to ARA ratio of 0.5:1 and 1:1, but not the group fed a ratio
282 of 1.5:1, performed significantly better than the no LCPUFA group. Brain evoked response potentials to a test
283 of inhibition (Go-No Go task) at 5.5 years and brain imaging studies at 9 years were consistent with these
284 results (48, 49).

285 While the study did not include a group that received DHA without ARA, these results show that a formula
286 providing nearly 1% DHA and close to 0.7% ARA - and thus less ARA than DHA - was generally ineffective
287 compared to formulas providing at least as much ARA as DHA. These data reinforce the concern about the
288 safety of feeding infants high levels of DHA without providing adequate amounts of ARA.

289

290 **Parents' expectations**

291 Representatives of the parent organization European Foundation for the Care of Newborn Infants (EFCNI)
292 emphasized that feeding their babies is one of the fundamental tasks for all parents; it is necessary to sustain
293 life and it is necessary to support optimal growth and development. Too often parents are judged by the
294 success or otherwise of their ability to feed their child and the process of feeding. The decisions surrounding
295 the task can be a source of enormous stress for mothers and fathers alike.

296 Today's parents are better educated, better informed and have a greater understanding of the importance of
297 the first 1000 days of an infant's life for long-term outcomes. While the decision to breastfeed or not may
298 depend on circumstances or choice, the expectations regarding the choice of an infant formula are the same.
299 Every parent wants to keep their child safe and protect them from harm. As formulas for infants are the only
300 processed foodstuff which must meet *all* nutritional requirements of the infant until appropriate
301 complimentary feeding can be established, it is critical that there is full confidence by all concerned
302 regarding the purity of the ingredients, the appropriate composition of the formulas, and the expected
303 health outcomes. Families are often confused about the differences between the various infant formulas
304 available on the market. The assumption and expectation by families is that the infant formula products on
305 offer have been thoroughly tested in preclinical and clinical settings. They expect that the decision to modify
306 formula composition is risk free and strictly regulated by regulatory bodies, that the manufacturing process
307 is strictly controlled and that the industry has learned from the mistakes of the past.

308 Whilst the above considerations do not take account of the barriers and difficulties faced by researchers in
309 meeting the expectations of families, it is important that researchers, industry, learned societies and
310 regulatory bodies strive to meet the parental expectations regarding first infant formula to achieve optimal
311 health and development outcomes, whilst maintaining the highest standard of safety.

312

313 **Conclusions**

314 The new European regulation on infant and follow-on formulae (7) stipulates that ingredients other than
315 those covered by the regulation may only be added to infant or follow-on formulae if the suitability and
316 safety of such additions have been demonstrated by appropriate studies, following the guidance of scientific
317 experts (50-54). The authors fully agree with this principle; however, in addition they also strongly support
318 that other major modifications of the composition of infant or follow-on formulae that have no documented
319 history of safe use need to be scientifically evaluated in pre-clinical and generally also in clinical studies. The
320 need for such evaluation is underlined by the tragic experience of induction of severe adverse health effects
321 in infants fed formula with modified composition without the addition of any new ingredients, e.g. due to
322 reduced contents of sodium chloride or of thiamine that both lead to serious adverse effects on health and
323 brain development (55-57).

324 The European regulation on infant and follow-on formulae (7) proposes a novel composition with mandatory
325 content of relatively high DHA concentrations (20-50 mg/100kcal, equivalent to about 0.5-1 % of fatty acids)
326 but no requirement to provide ARA. This novel infant formula composition has not been evaluated in infants
327 born at term, and there is no accountable data to document the suitability and safety of this novel concept
328 of infant formula composition in healthy infants. This proposed formula composition deviates markedly both
329 from the usual composition of human milk, which has never been found to provide DHA without ARA, and
330 from the composition of formula with added LC-PUFA as evaluated in many clinical trials and as used for
331 about two decades in Europe and in many other countries around the world. Moreover, studies reviewed
332 above indicate that the provision of high DHA intakes without balanced amounts of ARA may induce
333 undesirable effects in infants, such as reduced ARA levels in brain tissue, suboptimal neurodevelopment and
334 potentially also adverse effects on growth and immune development (58). Under conditions where scientific
335 evidence cannot resolve uncertainty regarding possible risks for exposed populations, the precautionary
336 principle is applied to prevent harm (59, 60). Therefore, we recommend that infants should not be fed
337 formula with high DHA contents but without ARA unless a thorough evaluation of this novel approach has
338 been performed and evaluated by independent scientific experts.

339

340 **Recommendations for the composition of infant and follow-on formula**

341 Based on the available information, we recommend that all infant formula and follow-on formula should
342 provide both DHA and ARA. The DHA content in formulae for infants should equal at least the mean content
343 in human milk globally (0.3 % of fatty acids) but preferably reach a level of 0.5 % of fatty acids, equivalent to
344 the mean + 1 SD content in human milk globally (1), to cover higher needs of some subgroups of infants, for
345 example due to variation in genes encoding enzymes mediating polyunsaturated fatty acid metabolism. This
346 level of 0.5 % DHA is also equivalent to intakes reported to provide functional benefit in several clinical
347 studies (61). While the minimal or optimal intake levels of ARA in infancy remain to be defined, and current
348 evidence does not allow determining an optimal ratio of ARA to DHA in the infant diet, we strongly
349 recommend that ARA should be provided along with DHA. At current formulas DHA levels up to about 0.64%
350 (47) we support the recommendation of the Codex Alimentarius that ARA contents in formulae for infants
351 should be at least equal to the contents of DHA (19).

352 Breast milk DHA in high fish-eating regions such as Japan may contain more than 1% DHA. Formulas that
353 replicate these higher DHA levels and with ARA levels above 0.7% ARA have not been tested; these should be
354 clinically evaluated prior to market introduction. Well-designed clinical studies should evaluate the optimal
355 intakes of DHA and ARA in infants at different ages based on relevant clinical outcomes, such as safety,
356 growth, neurodevelopment, and immune development. The second half of the first year of life deserves
357 specific attention since common weaning foods during this period generally provide only small amounts of
358 DHA and ARA. We recommend investment of public research funding to enable the execution of adequately
359 designed and powered clinical studies.

360

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369

370 **Contribution of authors**

371 BK and SEC drafted the manuscript, all authors reviewed the manuscript, contributed to the revision and
372 approved the final manuscript.

373

374 **Declaration of interests**

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